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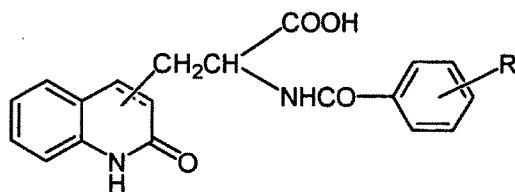
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[Item]	Description	1
[Item]	Abstract	1
[General Power of Attorney No.]		0311699

[Document Name] CLAIMS

[Claim 1] A pharmaceutical composition for accelerating salivation, which comprises as an active ingredient a carbostyryl compound of the formula:

[Chemical formula 1]



wherein R is a halogen atom, and the substitution position of the substituent on said carbostyryl nucleus is the 3- or 4-position, and the bond between the 3- and 4-positions of the carbostyryl nucleus is either a single bond or a double bond, or a salt thereof.

[Claim 2] The pharmaceutical composition for accelerating salivation according to claim 1, wherein the active ingredient is 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof.

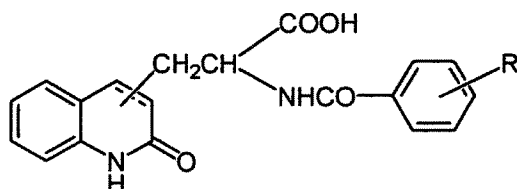
[Document Name] DESCRIPTION
 [Title of Invention] PHARMACEUTICAL COMPOSITION FOR
 ACCELERATING SALIVATION

[TECHNICAL FIELD]

[0001]

The present invention relates to a pharmaceutical composition for accelerating salivation. More particularly, the present invention relates to a pharmaceutical composition for accelerating salivation, which comprises as an active ingredient a carbostyryl compound of the formula (1):

[Chemical formula 1]



wherein R is a halogen atom, and the substitution position of the substituent on said carbostyryl nucleus is the 3- or 4-position, and the bond between the 3- and 4-positions of the carbostyryl nucleus is either a single bond or a double bond, or a salt thereof, or preferably comprises as an active ingredient 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof.

[BACKGROUND ART]

[0002]

Saliva plays an important role in the maintenance of the oral environments and the oral functions. Namely, there are two functions of saliva of dietary intake function and a function of maintaining the oral environments. With respect to the dietary intake function of saliva, saliva exhibits a digesting action such as formation of alimentary bolus and digestive enzyme action, or an activity of maintaining taste sensation through solubilization of tastant or secretion of gasticin. With respect to the function of maintaining oral environments, saliva exhibits self-cleaning effect on the teeth or the mucous membranes, recalcification action of the teeth, antibacterial action, immunization action, tissue repair promoting action by growth factors, etc., and antiinflammatory action.

Recently, there is an increase in the number of the patients, who

suffer from hyposalivation caused by various factors. Therefore, the social demand for treatment thereof has been increased. Hyposalivation has been found being accompanied by abnormality of salivary gland per se caused by radiation therapy or parotiditis, as well as by metabolic diseases (e.g., Basedow's disease, diabetes mellitus, etc.), or other diseases such as collagen diseases, and further hyposalivation is caused by stress factors or side effects of various medicines. In the recent aging society, the function of salivary gland is decreased by aging, and various medications for various complicated diseases supervened in the aging people are done, and as a result, it has been considered that a number of patients suffering from hyposalivation would be increased more than ever in future.

In hyposalivation, the tongue is reddened, and sometimes has a crack due to dryness of the oral cavity, by which a patient of hyposalivation complains of a pain when eating, and further complains of difficulty with chewing or swallowing. Further, it is known that hyposalivation causes uncomfortable feeling in the oral cavity, or taste disorders and articulation disorder, and further causes denture unstability, tooth caries, onset of alveolar blennorrhoea, mouth inflammation, pneumonia, and digestive dysfunction.

The topical application of artificial saliva is employed as a treatment of hyposalivation, but the effect thereof is temporary and limited. Anethole trithione and cevimeline hydrochloride are used as a salivation accelerator, but they have some defects, for example, the effects thereof are unstable and there is a problem of possible side effects. Under these circumstances, a new medicament for treatment of hyposalivation has been strongly desired.

[0003]

The carbostyryl compounds of the above formula (1) and a process for preparation thereof are disclosed in Patent Literature 1, and this literature also discloses that these compounds are useful as an antiulcer agent. It has also been disclosed that these carbostyryl compounds of the present invention are useful in the treatment of various diseases, for example, as an agent for treatment of gastric inflammation (cf., Patent Literature 2), or as an antidiabetic (cf., Patent Literature 3). Further, it has also been disclosed that these compounds exhibit a somatostatin

increasing activity or an activity of inhibiting somatostatin reduction (cf., Patent Literature 4). In addition, it has also been disclosed that these compounds are useful as an agent for protecting intestinal mucosa disorder (cf., Patent Literature 5), as a urease inhibitor (cf., Patent Literature 6), as an interleukin-8 inhibitor (cf., Patent Literature 7), as a cancer inhibitor (cf., Patent Literature 8), and as an agent for treatment of eye diseases (cf., Patent Literature 9). Furthermore, the carbostyryl compounds are disclosed to be useful as an inhibitor of ADP-ribosylation (cf., Patent Literature 10), as an agent for treatment of intravital toxin-type bacterial infection (cf., Patent Literature 11), and as an NADase inhibitor (cf., Patent Literature 12).

[Patent Literature 1]	JP-B-63-35623
[Patent Literature 2]	JP-A-3-74329
[Patent Literature 3]	JP-A-5-148143
[Patent Literature 4]	JP-A-6-509587
[Patent Literature 5]	JP-A-6-211662
[Patent Literature 6]	JA-A-7-101862
[Patent Literature 7]	JP-A-8-12578
[Patent Literature 8]	JP-A-9-71532
[Patent Literature 9]	JP-A-9-301866
[Patent Literature 10]	JP-A-10-231246
[Patent Literature 11]	JP-A-10-231247
[Patent Literature 12]	JP-A-11-228413

[DISCLOSURE OF INVENTION]

[PROBLEMS TO BE SOLVED BY INVENTION]

[0004]

As mentioned above, the decrease in salivation function may be a serious problem in view of oral sanitation, and further in order to improve the quality of life of the elderly people, a number of which has been drastically increased, and hence, it has been desired to develop a more effective salivation accelerator.

[MEANS FOR SOLVING THE PROBLEMS]

[0005]

The present inventors have intensively studied in order to find a new medicament for accelerating salivation, and as a result, they have

found that the carbostyryl compounds of the above formula (1), especially 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid, or a salt thereof exhibits a salivation accelerating activity, and finally have accomplished the present invention.

Namely, an object of the present invention is to provide a pharmaceutical composition for accelerating salivation comprising as an active ingredient a carbostyryl compound of the above formula (1) or a salt thereof, which is especially useful in the prophylaxis or treatment of a patient suffering from hyposalivation. The pharmaceutical composition of the present invention includes the following embodiments.

[0006]

1. A pharmaceutical composition for accelerating salivation, which comprises as an active ingredient a carbostyryl compound of the formula (1) or a salt thereof.
2. A pharmaceutical composition for accelerating salivation other than a pharmaceutical composition for mouth wash, which comprises as an active ingredient a carbostyryl compound of the formula (1) or a salt thereof.
3. A pharmaceutical composition for accelerating salivation for systemic administration, which comprises as an active ingredient a carbostyryl compound of the formula (1) or a salt thereof.
4. The pharmaceutical composition for the above 3, wherein the pharmaceutical composition for systemic administration is one for oral administration.
5. The pharmaceutical composition for the above 3, wherein the pharmaceutical composition for systemic administration is an injection preparation.
6. The pharmaceutical composition for accelerating salivation according to any one of the above 1 to 5, wherein the active ingredient is 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or a salt thereof.
7. The pharmaceutical composition for accelerating salivation according to any one of the above 1 to 5, which is a medicament for prophylaxis or treatment of xerostomia.
8. The pharmaceutical composition for accelerating salivation according to the above 6, which is a medicament for prophylaxis or

treatment of xerostomia.

[0007]

The pharmaceutical composition for accelerating salivation of the present invention comprises as an active ingredient the carbostyryl derivative of the above formula (1) or a salt thereof, and may be formulated into a conventional pharmaceutical preparation.

The pharmaceutical preparation is formulated by using conventional pharmaceutically acceptable diluents or carriers such as fillers, thickening agents, binders, wetting agents, disintegrators, surfactants, lubricants, and the like. The pharmaceutical preparations can be selected from various forms in accordance with the desired utilities, and the representative forms are tablets, pills, powders, solutions, suspensions, emulsions, granules, capsules, suppositories, injections (solutions, suspensions, etc.), aerosols, syrups, and the like. In addition, the present pharmaceutical composition can be prepared in admixture with a resin so that the sustained-release property can be increased. The pharmaceutical composition for accelerating salivation of the present invention is preferably prepared in the form of a pharmaceutical composition for systemic administration, particularly in the form of a pharmaceutical composition for oral administration such as tablets, pills, powders, solutions, suspensions, emulsions, granules, syrups, capsules, and the like.

[0008]

In order to form in tablets, there are used well known pharmaceutically acceptable carriers such as vehicles (e.g., lactose, white sugar, sodium chloride, glucose, urea, starch, xylitol, mannitol, erythritol, sorbitol, calcium carbonate, kaolin, crystalline cellulose, silicic acid, etc.), binders (e.g., water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate, polyvinylpyrrolidone, etc.), disintegrators (e.g., dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogen carbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium laurylsulfate, stearic monoglyceride, starches, lactose, etc.), disintegration inhibitors (e.g., white sugar, stearin, cacao butter, hydrogenated oils, etc.), absorption promoters (e.g., quaternary ammonium

base, sodium laurylsulfate, etc.), wetting agents (e.g., glycerin, starches, etc.), adsorbents (e.g., starches, lactose, kaolin, bentonite, colloidal silicates, etc.), lubricants (e.g., purified talc, stearates, boric acid powder, polyethylene glycol, etc.), and the like. Moreover, the tablets may also be in the form of a conventional coated tablet, such as sugar-coated tablets, gelatin-coated tablets, enteric coating tablets, film-coating tablets, or double or multiple layer tablets.

[0009]

In the preparation of pills, the conventional pharmaceutically acceptable carriers can be used and include, for example, vehicles (e.g., glucose, lactose, starches, cacao butter, hydrogenated vegetable oils, kaolin, talc, etc.), binders (e.g., gum arabic powder, tragacanth powder, gelatin, ethanol, etc.), disintegrators (e.g., laminaran, agar, etc.) and the like. In the preparation of suppositories, the conventional pharmaceutically acceptable carriers can be used, and include polyethyleneglycol, cacao butter, higher alcohols, esters of higher alcohols, gelatin, semi-synthesized glyceride, etc. Capsules can be prepared by charging a mixture of the active ingredient and the above carriers into hard gelatin capsules, soft capsules or hydroxypropylmethyl cellulose capsules (HPMC capsules) in usual manner.

[0010]

In the preparation of injections, the preparations are preferably in the form of solutions, emulsions or suspensions, and these preparations may be usually sterilized, and preferably in isotonic with the blood. When formulating into solutions, emulsions or suspensions, any conventional diluents which are usually used in this field can be used, and examples thereof are water, ethyl alcohol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, polyoxyethylene sorbitan fatty acid esters, etc. In order to prepare an isotonic solution preparation, it may additionally contain sodium chloride, glucose or glycerin in an amount being sufficient for this purpose. In addition, conventional solubilizer, buffering agents, or soothing agents may be added, and if necessary, coloring agents, preservatives, flavors, sweetening agents, or other medicaments may be added thereto.

[0011]

Aerosol preparations may usually be prepared by preparing a sterilized solution or suspension preparation, followed by mixing with an aerosol propellant. In the preparation of these solution or suspension preparations, any conventional diluents may be used therein, and examples thereof are ones as exemplified for the above injection preparations. The aerosol propellant may be any conventional ones, and examples thereof are chlorofluorocarbons (e.g., Freon 12, etc.), liquified gas propellants (e.g., Freon 123, etc.), or compressed gas propellants (e.g., nitrogen gas, carbon dioxide gas, etc.). In addition, these aerosol preparations may further contain conventional solubilizers, buffering agents, etc., and further contain, if necessary, coloring agents, preservatives, fragrances, flavors, sweetening agents, etc.

[0012]

The amount of the carbostyryl derivative (1) or a salt thereof to be incorporated into the pharmaceutical composition of the present invention is not specified but may be selected from a broad range, but usually, it is preferably in the range of about 1 to 70 % by weight, more preferably in the range of about 5 to 50 % by weight, based on the whole weight of the composition. In the particularly preferable pharmaceutical composition for accelerating salivation for oral administration, the amount of the active compound (1) or a salt thereof is preferably in the range of about 0.005 to 5 % by weight, more preferably in the range of 0.01 to 3 % by weight, based on the whole weight of the composition.

The suitable method for administration of the present composition may be determined in accordance with various forms of preparations, ages, sexes and other conditions of the patients, the degree of severity of diseases, and the like. For example, tablets, pills, solutions, suspensions, emulsions, granules, syrups and capsules are administered orally. Injections preparations are administered intravenously alone or in admixture with a conventional fluid replacement such as glucose solution or amino acid solution, and if necessary, injection preparations are administered alone intramuscularly, intracutaneously, subcutaneously, or intraperitoneally. Suppositories are administered rectally.

[0013]

The dosage of the medicament of the present invention may be

selected in accordance with the administration routes, ages, sexes and other conditions of the patients, the degree of severity of the diseases, and the like, but the amount of the carbostyryl derivative (1) or a salt thereof is usually in the range of 0.01 to 50 mg/kg of body weight per day. In addition, the active ingredient may be contained in the range of 1 to 1000 mg per single dosage unit.

[EFFECTS OF INVENTION]

[0014]

The pharmaceutical composition for accelerating salivation of the present invention can promote the saliva secretion by administering to a patient of hyposalivation, so that the present pharmaceutical composition can be useful as a medicament for prophylaxis or treatment of dry mouth, and xerostomia or hyposalivation, which may cause various oral diseases such as burning sensation of the mouth, taste disorder, glossalgia, periodontal diseases, and the like.

[BEST MODE FOR CARRYING OUT THE INVENTION]

[0015]

The pharmaceutical composition for accelerating salivation of the present invention may be prepared and used in various forms as mentioned above, and the present invention is illustrated by the following Examples, but should not be construed to be limited thereto.

[EXAMPLES]

[0016]

The pharmaceutical composition for accelerating salivation of the present invention and the effects thereof are illustrated in more detail by the following Preparations and Pharmacological Experiments.

[0017]

Preparation 1

2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)-propionic acid	150 g
Avicel (Trade Mark, manufactured by Asahi Kasei Corporation)	40 g
Corn Starch	30 g
Magnesium stearate	2 g

Hydroxypropyl methylcellulose	10 g
Polyethylene glycol-6000	3 g
Castor Oil	40 g
Methanol	40 g

The active compound of the present invention, Avicel, corn starch and magnesium stearate are mixed and kneaded and the mixture is tabletted by using a conventional pounder (R 10 mm) for sugar coating. The tablets thus obtained are coated with a film coating agent consisting of hydroxypropyl methylcellulose, polyethylene glycol-6000, castor oil and ethanol to give film-coating tablets.

[0018]

Preparation 2

2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)-propionic acid	150 g
Citric acid	1.0 g
Lactose	33.5 g
Dicalcium phosphate	70.0 g
Pullonic F-68	30.0 g
Polyvinylpyrrolidone	15.0 g
Polyethylene glycol (Carbowax 1500)	4.5 g
Polyethylene glycol (Carbowax 6000)	45.0 g
Corn starch	30.0 g
Dry sodium laurylsulfate	3.0 g
Dry magnesium stearate	3.0 g
Ethanol	q.s.

[0019]

The active compound of the present invention, citric acid, lactose, dicalcium phosphate, Pullonic F-68 and sodium laurylsulfate are mixed.

The mixture is screened with No. 60 screen and is granulated with an alcohol solution containing polyvinylpyrrolidone, Carbowax 1500 and Carbowax 6000. If required, an alcohol is added thereto so that the powder mixture is made a paste-like mass. Corn starch is added to the mixture and the mixture is continuously mixed to form uniform particles. The resulting particles are passed through No. 10 screen and entered into a tray and then dried in an oven at 100°C for 12 to 14 hours. The dried particles are screened with No. 16 screen and thereto are added dry sodium laurylsulfate and dry magnesium stearate, and the mixture is tabletted to form the desired shape.

The core tablets thus prepared are varnished and dusted with talc in order to guard them from wetting. Undercoating is applied to the core tablets. In order to administer the tablets orally, the core tablets are varnished several times. In order to give round shape and smooth surface to the tablets, further undercoating and coating with a lubricant are applied thereto. The tablets are further coated with a coloring coating material until the desired colored tablets are obtained. After drying, the coated tablets are polished to obtain the desired tablets having uniform gross.

[0020]

Preparation 3

2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid	5 g
Polyethylene glycol (Molecular weight: 4000)	0.3 g
Sodium chloride	0.9 g
Polyoxyethylene sorbitan monooleate	0.4 g
Sodium metabisulfite	0.1 g
Methyl paraben	0.18 g
Propyl paraben	0.02 g
Distilled water for injection	10.0 ml

[0021]

The above parabens, sodium metabisulfite and sodium chloride are dissolved in the about half volume of the above distilled water with stirring at 80°C. The resulting solution is cooled to 40°C, and the present compound, and then polyethylene glycol and polyoxyethylene sorbitan monooleate are dissolved with this solution. Then, distilled water for injection is added to the resulting solution, and the final volume of the mixture is adjusted. The solution thus obtained is sterilized by filtration through a suitable filter paper to give an injection preparation.

[Experiment 1]

[0022]

The effects of the present active compound on salivation in anesthetized rats were studied as mentioned below.

[0023]

Method of Experiment:

1) Preparation of experimental models:

Models for studying salivation were prepared according to the method of Masunaga, et al. (Masunaga, H., et al., Long-lasting salivation induced by a novel Muscarinic receptor agonist SNI-201 in rats and dogs. *Eur. J. Pharmacol.*, 339: 1-9, 1997).

Namely, rats had been fasted from the day before the experiment except that the intake of water was freely allowed, and the rats were anesthetized with Nembutal. The rats were put down on the back, and the neck was subjected to midline incision. An ATOM amniotic fluid suction catheter of 6Fr. was inserted to the air tube in order to keep the airway clear. Next, a polyethylene tube (SP55 Natsume) containing a solution of 10 μ /ml heparin in physiological saline was inserted into the carotid artery for administration of a medicament.

2) Measurement of the salivation amount:

A 0.03 mg/ml or 0.1 mg/ml solution of the test compound (2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid; general name: Rebamipide) in 2 % aqueous sodium hydrogen carbonate solution, and a vehicle (2 % aqueous sodium hydrogen carbonate solution) as a control solution were used, and the test compound solution and the control solution in an amount of 1 mL/kg were respectively administered intravenously via the polyethylene tube inserted into the carotid artery.

Then, the salivation amount was measured every 10 minutes for 20 minutes with using cotton swabs, and the salivation amount per one minute was calculated from the total salivation amount for this period.

In this measurement, the salivation amount was measured in such a way that the dried cotton swab (the weight thereof was previously measured) was inserted into the mouth of rat, and the swab was exchanged with a new dried one in every ten minutes, and the total salivation amount was calculated from the difference in the weight of the swab between before and after inserting into the mouth.

[0024]

Results:

The average salivation amount was calculated as measured in the vehicle-treated group (5 animals), the test compound (0.03 mg/kg)-treated group (5 animals) and the test compound (0.1 mg/kg)-treated group (4 animals), and the percentage of the average salivation amount in the test compound-treated groups against that of the vehicle-treated group was calculated. The results are shown in Table 1.

As shown in Table 1, the average \pm standard error of the salivation amount in the vehicle-treated group was 0.128 ± 0.008 mg/min ($n = 5$), while those of the test compound (0.03 mg/kg)-treated group and the test compound (0.1 mg/kg)-treated groups were 0.262 ± 0.084 mg/min ($n=5$) and 0.305 ± 0.097 mg/min ($n=4$), respectively. Thus, by intravenously administering a test compound in an amount of 0.03 or 0.1 mg/kg, it was observed that the salivation amount was increased by 205 % and 239 %, respectively, in comparison with the vehicle-treated control group.

[0025]

[Table 1]

	Salivation amount	
	(mg/min)	(%)
Vehicle-treated Group (n=5)	0.128 ± 0.008	100
Test compound (0.03 mg/kg)-treated Group (n=5)	0.262 ± 0.084	205
Test compound (0.1 mg/kg)-treated Group (n=4)	0.305 ± 0.097	239

The salivation amount is expressed by the measured value (mg/min) in the average \pm standard error, and the comparison with the vehicle-treated group is expressed by %.

[0026]

Conclusion:

As is apparent from the above results, the salivation amount was dose-dependently increased by intravenous administration of a test compound in anesthetized rats. Thus, it was proved that the test compound exhibits an activity of accelerating salivation by systemic administration.

[Experiment 2]

[0027]

The effects of the present active compound by intragastric administration in non-anesthetized rats with respect to the salivation were studied as mentioned below.

[0028]

Method of Experiment:

Using non-anesthetized rats, the saliva being swallowed for 4 hours on awaking into the diverticulum placed at the esophagus was collected and the salivation amount (g) was measured.

Vehicle (0.5% sodium carboxymethyl cellulose solution) or Rebamipide 10, 30 or 100 mg/kg was intragastrically administered once when the esophagus diverticulum was set, and as a result, the average \pm standard error of the salivation amount was 0.88 ± 0.23 g (n=7) in the vehicle-treated group, 0.99 ± 0.21 g (n=8) in the Rebamipide (10 mg/kg)-treated group, 1.37 ± 0.26 g (n=7) in the Rebamipide (30 mg/kg)-treated group, and 1.72 ± 0.40 g (n=8) in the Rebamipide (100 mg/kg)-treated group.

[0029]

Conclusion:

As is apparent from the above results, the salivation amount was dose-dependently increased by intragastrical administration of Rebamipide in non-anesthetized rats. Thus, it was proved that the active compound of the present invention exhibits an accelerating activity of salivation by intragastrical administration.

[INDUSTRIALY APPLICABILITY]

[0030]

The pharmaceutical composition for accelerating salivation of the present invention is useful in the prophylaxis and/or treatment of patients suffering from hyposalivation, for example, patients showing symptoms or general symptoms such as dry mouth caused by viscous feeling of saliva or viscosity promotion, etc., or oral burning; taste disorder; difficulty of food intake such as swallowing dysfunction; glossalgia or pain of the oral mucous membrane such as erythema of the tongue, atrophy of tongue papilla, smooth tongue, etc.; fragile of the oral mucous membrane; disorders caused by reduction of self-cleaning function such as angulus infectiosus, candida, tooth caries, highly onset of tooth caries, periodontal disease, oral mucosa diseases, ill-fitting denture, denture ulcer.

Especially, hyposalivation has many symptoms such as dehydration, elevated temperature or mouth respiration caused by stress, drying, fever or severe vomiting or diarrhea, or hyposalivation may onset in the middle of the treatments, for example, caused by side effects of a medicine, radiation therapy, or surgical excision of salivary gland. Further, the present pharmaceutical composition is useful in the prophylaxis and/or treatment of xerostomia or hyposalivation accompanying Sjögren's syndrome, rheumatoid arthritis, hidebound disease, multiple myositis, systemic lupus erythematosus, diabetes mellitus, kidney failure, diabetes insipidus, nerve injury, loss of mastication function, senile atrophy of salivary gland.

[Document Name] ABSTRACT

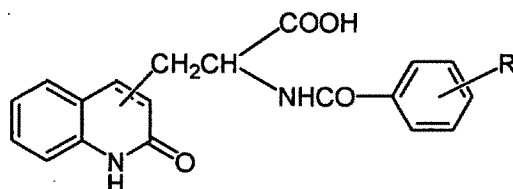
[Abstract]

[Subject]

The present invention provides a novel pharmaceutical composition for accelerating salivation.

[Means for solution]

Novel pharmaceutical composition for accelerating salivation, which comprises as an active ingredient a carbostyryl compound of the formula:



wherein R is a halogen atom, and the substitution position of the substituent on said carbostyryl nucleus is the 3- or 4-position, and the bond between the 3- and 4-positions of the carbostyryl nucleus is either a single bond or a double bond, or a salt thereof.

The pharmaceutical composition of the present invention exhibits an accelerating activity of salivation, and is useful in the prophylaxis or treatment of xerostomia or hyposalivation.

[Selected figure] Nil

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APPROVED OR SUPPLEMENTED INFORMATION

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[Payment of Fees]	
[Prepayment Book No.]	223643
[Amount to be paid]	4,200 yen
[List of attached documents]	
[Item]	Power of Attorney 1
[Indication of Referred Item]	General Power of Attorney submitted on May 14, 2004

APPROVED OR SUPPLEMENTED INFORMATION

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APPLICANT RECORD

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1. Date of Registration August 27, 1990
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APPLICANT RECORD

Identification No. [596165589]

1. Date of Registration November 15, 1996
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